REMARKS

I. STATUS OF THE CLAIMS

Claims 63-104 and 108-112 are pending and under examination. Claims 1-62 and 105-107 were canceled previously, without prejudice or disclaimer. Applicants reserve the right to file one or more continuing applications to the canceled subject matter.

Claims 63, 64, 69, 74, 79, 84, 89, 94, 100, 101, 103, 104, 108, 109, 110, 111, and 112 are amended.

Claims 63, 64, 69, 74, 79, 84, 89, 94, 100, and 101 are revised to comport with Examiner Kaufman's helpful suggestion to replace "single substance without forming a polymer" with the recitation that "said antibody or functional fragment thereof is free of any polymeric forms," as indicated at page 7 of the Office Action.

Claims 103 and 104 are amended to delete "prophylactic or."

Claim 108 is amended in step (ii) to make clear that the step of obtaining monoclonal antibodies means obtaining "monomeric" antibodies that also induce apoptosis in response to Examiner Kaufman's helpful suggestions at page 6 of the Office Action.

Other remaining claims have been amended to delete "calculates" which is duplicative of "calculated" and to replace "antibody *and* the functional fragment" with "antibody *or* the functional fragment."

Since none of these claims introduces new matter, and since they comport with Examiner Kaufman's suggestions, Applicants request their entry into the record.

II. WITHDRAWN REJECTIONS

Applicants thanks Examiner Kaufman for indicating at page 2 of the Office Action that rejection are withdrawn of claims 63-104 and 108 as anticipated under 35 U.S.C. § 102(b) by U.S. Patents No. 7,244,429 and No. 6,342,369.

Also withdrawn are the rejections of claims 63-104 under Section 112, first paragraph, due to allegedly new matter; and all other rejections under Section 112, second paragraph, for written description issues.

IV. SPECIFICATION

The Office asserts that Tables 1 and 2 on page 56 "show[] no information because all the symbols for cross-reactivity are identical." Office Action at page 2. Applicants are confused by this statement. Table 1 shows that all of the listed antibodies react to TRAIL-R1 (as denoted by the "+" symbol) and none of them reacted to TRAIL-R2 (denoted by the "-" symbol). Accordingly, the symbol in each column (TRAIL-R1 vs. TRAIL-R2) are identical for each antibody entry because the factual results demonstrated the TRAIL-R1-specificity of named antibodies.

Table 2 likewise indicates that essentially all of the listed antibodies were reactive to TRAIL-R2 but not to TRAIL-R1. All of the antibody entries, therefore, save for A-4-29, KMTR1, andD1M, in Table 2 show a "+" symbol in the TRAIL-R2 column.

The Office also asserts that Tables 3 and 4 "do[] not use the symbols of the legend." Office Action at page 3. Applicants again are unsure what to make of this because the symbols within the column/row entries of Table 2 actually do use the "++", "+", and "-" symbols noted in the table legend to denote the reactivity status of each antibody.

Applicants in good faith believe there is nothing incorrect with any of Tables 1-4 and therefore kindly ask the Office to elaborate on the objections should they be maintained, or to call the undersigned to discuss this matter by phone.

Indefiniteness

Claims 63, 64, 69, 74, 79, 84, 89, 94, 100, 101, 102, and 108 are rejected under 35 U.S.C. § 112, second paragraph, for alleged lack of clarity. For the reasons set forth in the Status of the Claims above, Applicants submit that their amendments address each of the Office's concerns in this regard, as articulated by Examiner Kaufman at pages 6 and 7 of the Office Action. Accordingly, Applicants respectfully request withdrawal of each of these particular rejections.

V. CLAIM OBJECTIONS

Various claims are objected to because "when the claims were [last] amended, new words were added (underlining) without lining through the words intended to be deleted." Office Action at page 2.

Respectfully, Applicants indicated the deletion of short words, such as "that," "were," "is" and "the," in the claims using double brackets without strike-outs as permitted under 37 C.F.R. § § 1.121 (c)(2): "The text of any deleted matter must be shown by strike-through except that double brackets placed before and after the deleted characters may be used to show deletion of five or fewer consecutive characters." Accordingly, Applicants do not believe any correction is now required but would be grateful if Examiner Kaufman would elaborate on any amendments she believes to have been improperly effected.

VI. THE CLAIMS ARE ENABLED

Claims 63-104 and 108-112 are rejected under 35 U.S.C. § 112, first paragraph, for an asserted lack of enabling support in the specification for monoclonal antibodies other than 0304 and 0322, which are only present in monomeric form, and fragments thereof, respectively. Office Action at page 3. Thus, the Office is heard to acknowledge that the specification is enabling for MAbs 0304 and 0322 and their functional fragments. *Id.*

Applicants respectfully assert that the specification *also* is enabling for monoclonal antibodies other than 0304 and 0322. That this is the case is apparent from the inventors' discovery that antigenic TRAIL-R2 hybridoma cell lines produce monoclonal monomers

that have the recited apoptotic properties. At the time of the present invention, this *subclass* of antibodies was unknown and unrecognized by those of skill in the antibody field. Thus, the skilled person did not realize that hybridoma cells could be used to produce a subclass of anti-TRAIL-R2 monoclonal antibodies that are both monomeric and active in inducing cancer cell death.

It is a key aspect of the invention, therefore, that a distinct subpopulation of monoclonal antiboides, which the inventors discovered to be routinely obtainable, that need not polymerize with one another or act with some other exogenous factor(s) in order to induce cell death. For this reason, the inventors said: "we have . . . succeed[ed] for the first time in the world in producing a novel monoclonal antibody" that has "no side effect of inducing cytotoxicity against" normal hepatocytes, a problem with conventional anti-TRAIL-R2 antibodies (sentence beginning at the bottom of page 19 of the substitute specification, filed with the USPTO on June 7, 2004).

To briefly summarize, Applicants created a hybridoma and subjected the culture supernatant of that hybridoma to two different ELISA assays using microplate wells which had been coated with peptide fragments of the TRAIL-R2 extracellular domain region. See Examples 4 and 5 at pages 54 and 59, respectively. Applicants used different, horseradish peroxidase-labeled detection antibodies in the two different assays: in one they used goat anti-human Igκ antibodies (see Example 4, page 55, line 7); and in the other they used a series of sheep anti-human IgG antibody subclasses (IgG1, IgG2, IgG3, and IgG4) (see Example 5, page 59, lines 7-9), to ultimate detect the presence of TRAIL-R2-specific antibodies present in the culture supernatant.

Applicants subsequently purified the monoclonal antibodies from the supernatant (Example 21), and then *fractionated* the monoclonal antibody preparation (Example 27). Applicants then evaluated each of those antibody fractions for apoptosis-inducing activity in the presence or absence of a goat anti-human IgG(γ) polyclonal antibody (Example 28). This polyclonal antibody is a crosslinker which co-joins antibodies present in a fraction.

Due to this series of procedures, Applicants identified, in the fractions to which the polyclonal was not added, antibodies that existed as monomers but which still had apoptosis-inducing activity. See Example 28 at page 114: "it was revealed that not only the fractions containing dimer or multimer antibody . . . but also the fractions containing monomer . . . had the cell-death-inducing activity on Colo205 cells."

Applicants demonstrated that polymeric forms of another antibody, H-48-2, successfully induced apoptosis, but not the monomeric form of H-48-2. See Example 28, page 115. Yet, the test sample that contained the monomeric form plus the polyclonal antibody crosslinker, did induce apoptosis. *Id.* See also Example 29.

Accordingly, Applicants discovered a subclass of monomeric antibodies that are able to induce cell death without the need for crosslinkers or to naturally exist as polymers. Applicants also corroborated that the type of detection antibody that had been used to detect the presence of anti-TRAIL-R2 antibodies in the original ELISA assays. See the last line of Example 28 at page 116.

Applicants' specification is enabling precisely because it teaches the skilled person how to access, in routine fashion, the previously unrecognized subpopulation of monomerically-active, monoclonal antibodies that target TRAIL-R2 receptors, as presently recited. Thus, the enabling quality of the specification is manifested in its ample characterization of both the appropriate immunogenic stimulus (antigen) and the screening process that reproducibly yields a monoclonal antibody of the prescribed properties, rendering the endeavor routine of producing, identifying, and isolating monoclonal antibodies as claimed.

In particular, the skilled person is directed by Applicants' specification to screen a second time the antibody fraction of a particular hybridoma supernatant as described above. It is by way of these screening steps that the inventors identified and effectively accessed the category of *monomerically-active* monoclonals, which are presently claimed. While the prior art did not predict this distinct subclass of monoclonal antibodies, the skilled person, once so informed by Applicants' specification, could readily obtain

representatives of the subclass from the supernatant of a antigen-primed hybridoma cell line, as taught in the specification.

In other words, a straightforward reading this specification would have empowered the skilled person to apply otherwise conventional methodology, in conjunction with Applicants' described screening regime, to produce any number of molecules from the revealed subclass of monomerically-active monoclonal antibodies, optionally using other hybridomas expressing other TRAIL-R2 antigenic peptides to this end. That the results of this wholly routine experimentation, guided by Applicants' teachings, not only are reproducibly but also comport with the salient claim recitations is apparent from present Example 3 ("Preparation of human monoclonal antibodies against TRAIL-R1 and R2," page 50) and Example 17 ("Cell-death-inducing activity on carcinoma cells," page 101).

Example 3 describes how monoclonal antibodies can be prepared according to methods which are specifically raised against the extracellular region of TRAIL-R2, such as those set forth in Introduction of Experimental Protocols for Monoclonal Antibody (Monoclonal Antibody Jikken Sosa Nyumon, written by Tamie ANDO et al., KODANSHA, 1991). See paragraph bridging pages 50 and 51. Example 17 describes how the culture supernatant of the hybridoma producing the human anti-TRAIL-R2 monoclonal antibodies obtained from Example 3 can be evaluated for cell-death-inducing activity. In association with this, Table A-1 relates the cell-death-inducing activity of the supernatant of the hybridomas 0304 and 0322, which produce anti-TRAIL-R2 monoclonal antibodies that kill colon cancer cells. See pages 102 and 103. In Example 21 ("Preparation of each antibody," page 106) and Example 22 ("Cell-death-inducing activity on carcinoma cells by the purified human anti-TRAIL-R2 monoclonal antibody," page 107), moreover, Applicants provided experimental details and guidance for purifying monomeric monoclonal antibodies from the hybridoma supernatant and evaluating their ability to induce cell death

In view of these results and related teachings, there is no reasonable basis for questioning whether the described protocol can produce a third monoclonal antibody of the subclass discovered by Applicants, or a fourth or a fifth for that matter, even employing a different cell line/antigen combination from the ones detailed in the above-mentioned

examples. To the contrary, neither the level of effort involved nor the degree of predictability in outcome is "undue," but instead is endemic or routine to the field.

For these reasons, Applicants respectfully submit that the claimed invention is enabled, and they ask Examiner Kaufman to withdraw this rejection.

CONCLUSION

Applicants invite Examiner Kaufman to contact the undersigned directly, in the event that she believe any of the salient issues to warrant further consideration.

Respectfully submitted,

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The Commissioner is authorized to charge any additional fees, which may be required under 37 CFR §§ 1.16 - 1.17, and to credit any overpayment to Deposit Account No. 19-0741. Should no proper payment accompany this response, then the Commissioner is authorized to charge the unpaid amount to the same deposit account. If any extension is needed for timely acceptance of submitted papers, Applicants hereby petition for it under 37 CFR §1.136 and authorize payment of applicable fee(s) from the deposit account.